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# Early development of the metabolic syndrome after chemotherapy for testicular cancer

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**Background:** The metabolic syndrome (MS) might increase the risk of cardiovascular disease in testicular cancer (TC) survivors. We investigated its prevalence, development, vascular implications, and the role of gonadal function.

**Methods:** TC survivors treated with chemotherapy and follow-up  $\geq 3$  years ( $N = 370$ , study I) were retrospectively evaluated for the development of cardiovascular risk factors. A subgroup followed 3–20 years ( $N = 173$ , study II) was compared with controls ( $N = 1085$ ) for MS prevalence and evaluated for vascular function.

**Results:** In TC survivors (study I), 24% developed overweight, 24% hypercholesterolemia, and 30% hypertension, after median follow-up of 1.7, 0.9, and 5.1 years, respectively. At the median follow-up of 5 years (study II), 25% of survivors have the MS [odds ratio (OR) 2.2, [95% confidence interval (CI) 1.5–3.3] compared with controls]. Survivors with MS have features of inflammation and prothrombotic state, increased carotid artery intima-media thickness. Survivors with testosterone levels  $< 15$  nmol/l (22%) have an increased risk of the MS (OR 4.1, 95% CI 1.8–9.3).

**Conclusions:** The current data suggest that the MS occurs at earlier age in TC survivors treated with chemotherapy compared with controls and is accompanied by early signs of atherosclerosis. As low testosterone may have a causal role, it is a target for interventions.

**Key words:** cancer survivors, cisplatin, hypogonadism, metabolic syndrome, testicular cancer, vascular damage

## Introduction

Cardiovascular disease (CVD) is a frequent late effect after treatment of testicular cancer (TC) with an estimated 20-year risk of about 18% in Dutch TC survivors [1]. Coronary heart disease (CHD) is particularly common (estimated 20-year risk 10%) with approximately twofold increased risk of myocardial infarctions in nonseminomatous TC survivors with attained age  $< 55$  years [1]. Consequently, CVD represents a threat to life expectancy and quality of life of a large proportion of survivors. Both mediastinal radiotherapy [1] and platinum-based chemotherapy regimens [1, 2] are associated with increased CVD risk compared with treatment with surgery alone. This increased CVD risk may be related to accelerated atherosclerosis [3].

Platinum-based chemotherapy is associated with increased prevalence of excessive weight gain [4], dyslipidemia [5], hypertension [4, 5], and insulin resistance [5]. These factors are the core components of the metabolic syndrome (MS), which is associated with increased risk of atherosclerotic disease in the general population [6]. Central obesity with visceral adipose tissue deposition may have an important role. Its hyperlipolytic state and excess of free fatty acids contribute to insulin resistance. In addition, visceral adipose tissue produces proinflammatory and prothrombotic factors [6, 7].

Although the MS may represent the connection between the cancer treatment and the increased long-term CVD risk in cancer survivors, information on its prevalence compared with the general population, its etiology and development over time, and its effects on vascular function and the eventual development of overt CVD is scarce.

In this study, we present data on cardiovascular risk factors and the MS in long-term ( $\geq 3$  years) nonseminomatous TC survivors treated with platinum-based chemotherapy: the development over time of cardiovascular risk factors (study I), the prevalence of MS compared with the general male population, its associated features, and implications for

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vascular structure and function, and its relation to gonadal function (study II).

## methods

### patients

Patients were selected from our cohort of long-term survivors of disseminated nonseminomatous TC treated with platinum-based chemotherapy at University Medical Center Groningen, between 1977 and 2004 ( $N = 439$ ) (Figure 1). For the retrospective evaluation of the development of cardiovascular risk factors (study I), patients had to have a follow-up duration of  $\geq 3$  years. Patients with CHD [defined as myocardial infarction or coronary artery disease (proven by angiography, or by treatment with angioplasty or bypass surgery)] before the start of chemotherapy were excluded. The MS and its associated features (study II) were cross-sectionally assessed in a subgroup of study I. Inclusion criteria were attained age  $< 60$  years and follow-up of maximum 20 years. Exclusion criteria were history of cardiac disease before or after chemotherapy, radiotherapy to mediastinum, and participation in a previous study on cardiovascular risk profile [5]. The Ethics committee approved the study and participants gave written informed consent.

### control population

Control data concerning the MS in the general population were available from two studies: men aged 28–60 years representing the general male population in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study [8, 9] and, men aged 18–42 years participating as sibling controls to a study on late effects in childhood cancer survivors (CCS) [10]. Controls with a history of myocardial infarction or coronary artery disease were excluded. The resulting control group consisted of 1085

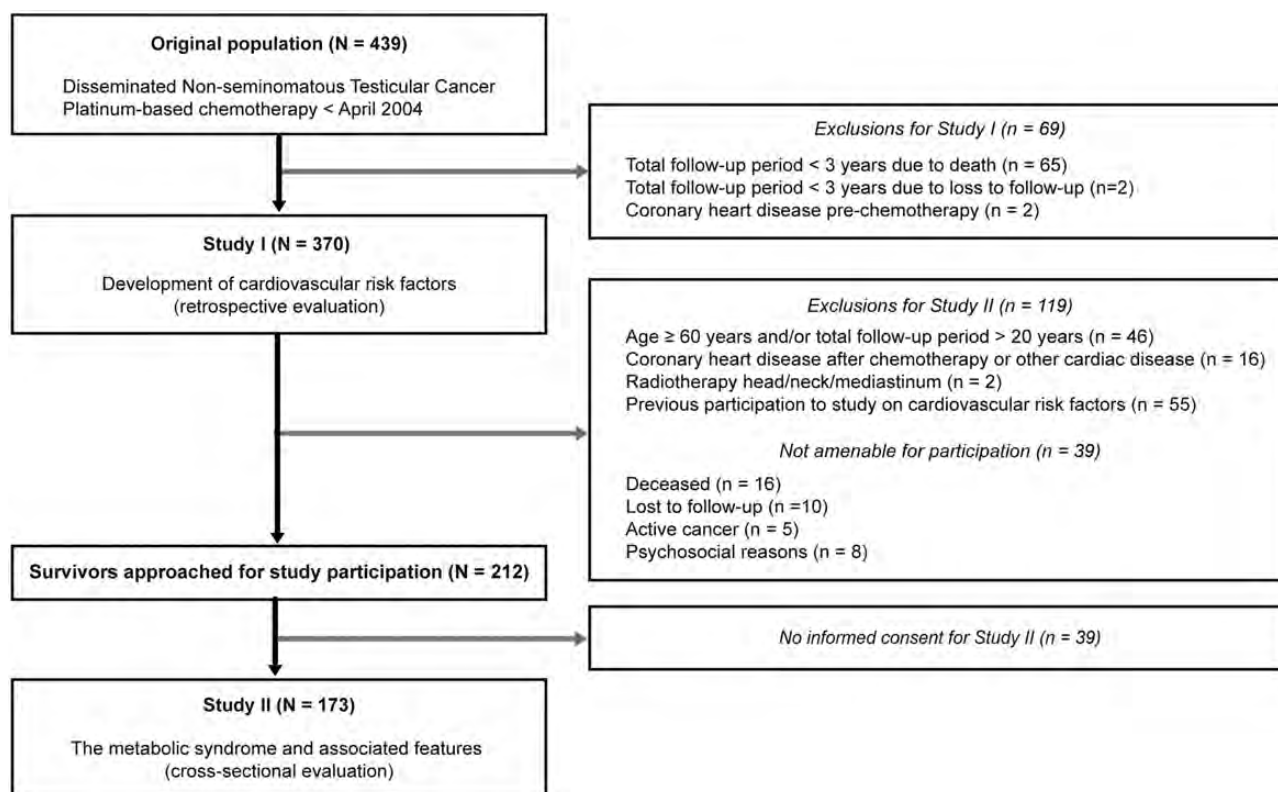
men (1020 from the PREVEND study and 65 from the CCS study) with cross-sectional data available on waist circumference, blood pressure, fasting lipid and glucose levels, and medication use, to allow for an evaluation of the MS. The median age of the controls was 44 years (range 18–59).

### evaluation of the development of cardiovascular risk factors (study I)

Medical records, updated from general practitioners' files, were evaluated for disease- and treatment-related characteristics and follow-up data. Cardiovascular risk factors were retrospectively evaluated for presence prechemotherapy and development during follow-up. With respect to overweight, body mass index [BMI;  $\text{weight}(\text{kg})/\text{height}(\text{m})^2$ ]  $> 27.8 \text{ kg/m}^2$  was recorded [11], and used in the early phase of establishment of the cohort [5]. Hypertension was defined as blood pressure systolic  $> 150$  mmHg and/or diastolic  $> 95$  mmHg [5, 12] and/or use of antihypertensive drugs, and hypercholesterolemia as nonfasting cholesterol levels  $> 6.5$  mmol/l at  $\geq 3$  separate time points and/or use of cholesterol-lowering drugs. Follow-up duration was calculated from the start of chemotherapy to the last assessment of each risk factor and in case of overweight, hypertension, or hypercholesterolemia also to date of this diagnosis.

### assessment of the metabolic syndrome and its associated features (study II)

Evaluation consisted of a medical history focused on medication use, smoking, and family history for CVD (positive in case of parent or brother/sister with CHD, cardiac death, or cerebrovascular accident at age  $< 60$  years) and assessment of weight, height, waist circumference (at umbilical level), hip circumference (at broadest part), and blood pressure.



**Figure 1.** Flow diagram of included patients.

Blood pressure was measured at the outpatient clinic in a supine position after a 10-min resting period.

Fasting blood samples were analyzed for HDL cholesterol and triglycerides (plasma), glucose (plasma), and insulin (serum). Leptin and adiponectin were determined by ELISA (#EZHL-80SK and #EZHADP-61K, Linco Research, St Charles, MO, EDTA Plasma). In addition, markers for inflammation, prothrombotic state, and endothelial activation were determined. High-sensitivity C-reactive protein (hsCRP, serum), fibrinogen, Von Willebrand factor (vWF) antigen, plasminogen activator type-1 (PAI-1) antigen, and tissue-type plasminogen activator (tPA) antigen (citrate plasma) were measured as described previously [3]. Urinary albumin excretion and creatinine clearance were determined from a 24-h urine sample [3].

For assessment of the MS, the American Heart Association/National Heart, Lung, and Blood Institute classification [13] was used with the presence of the MS in case of  $\geq 3$  of the following criteria: central obesity (waist circumference  $\geq 102$  cm), high triglycerides ( $\geq 1.7$  mmol/l or medication), low HDL cholesterol ( $< 1.03$  mmol/l or medication), high blood pressure (systolic  $\geq 130$  mmHg or diastolic  $\geq 85$  mmHg or medication), and high glucose ( $\geq 5.6$  mmol/l or medication). In addition, a waist/hip ratio was calculated as measure for central obesity, HOMA-IR index (fasting insulin (mU/l)  $\times$  fasting glucose (mmol/l)/22.5) for insulin resistance and a PAI-1/tPA ratio for prothrombotic state. Gonadal function was analyzed by measuring serum total testosterone, luteinizing hormone, and follicle-stimulating hormone.

As a measure of cardiovascular autonomic function, baroreflex sensitivity (BRS) at rest in supine position was determined [14]. To assess vascular structure and function, the intima-media thickness (IMT) of the common carotid artery was measured, and carotid distensibility, compliance, and stiffness calculated, as described previously [3].

## statistical methods

The cumulative risk for cardiovascular risk factors in TC survivors (study I) was plotted according to the Kaplan–Meier procedure. Presence of a risk factor at last assessment was considered an event, with follow-up duration

calculated from the start of chemotherapy to the diagnosis of the risk factor. When the risk factor was already present prechemotherapy, the follow-up duration was set to zero. Median follow-up until development of each risk factor was calculated for TC survivors in whom the risk factor developed after completion of chemotherapy.

The risk of the MS and its components in TC survivors (study II) was compared with the general population data by binary logistic regression analysis with adjustment for age.

TC survivors with MS were compared with survivors without MS with respect to associated features, vascular structure and function, and gonadal function using the nonparametric Mann–Whitney *U* test for continuous data and the  $\chi^2$ -test for categorical data. The association between MS and markers for vascular damage was further analyzed using linear regression analysis with MS as independent variable and adjustment for age. The effect of gonadal function on the risk of the MS and its components was tested with binary logistic regression analysis. Receiver-operator-characteristic (ROC) curve analysis was used to estimate the optimal cutoff value for total testosterone levels to differentiate between persons with and without MS.

Statistical analyses were carried out with SPSS for Windows 16.0 (SPSS Inc., Chicago, IL). For all analyses, a two-tailed *P* value  $< 0.05$  was considered significant.

## results

### study population characteristics

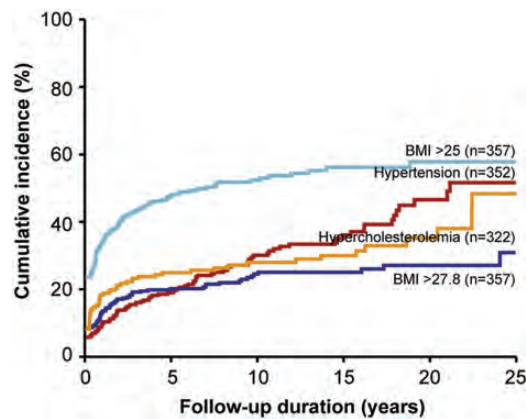
The original cohort of 439 nonseminomatous TC patients treated with platinum-based chemotherapy includes 370 patients without pretreatment history of CHD and with follow-up  $\geq 3$  years (study I) (Figure 1). From the subgroup of 212 patients approached for participation in the study on the MS (study II), 173 patients (82%) gave informed consent. Baseline disease- and treatment-related characteristics and follow-up data for the two study populations are shown in Table 1.

**Table 1.** Baseline characteristics and follow-up data of the TC patients in study I and the subpopulation included in study II

		Study I (N = 370)	Study II (N = 173)
Baseline characteristics			
Age at start chemotherapy (years)	Median (range)	28 (16–64)	28 (16–52)
Chemotherapy regimen <sup>a</sup>			
BEP/EP	N (%)	262 (71%)	159 (92%)
PVB		27 (7%)	0 (0%)
PVB+		42 (11%)	0 (0%)
PVB/BEP		15 (4%)	1 (1%)
Other		24 (7%)	13 (7%)
Follow-up data			
Follow-up duration (years)	Median (range)	12 (3–29)	5 (3–20)
Age at end follow-up (years)	Median (range)	42 (19–73)	37 (19–59)
Deceased	N (%)	25 (7%)	not applicable
Death of testicular cancer		14 (4%)	–
CHD	N (%)	19 (5%)	not applicable
Age at CHD (years)	Median (range)	49 (30–62)	–
Follow-up duration at CHD (years)	Median (range)	15 (0–28)	–

<sup>a</sup>CHD, coronary heart disease. Chemotherapy regimen: BEP, bleomycin, etoposide, cisplatin; EP, etoposide, cisplatin; PVB, cisplatin, vinblastin, bleomycin; PVB+, PVB followed by maintenance therapy with cisplatin and vinblastin; PVB/BEP, alternating courses of PVB and BEP; Other, CEB (carboplatin, etoposide, and bleomycin) or BOP/VIP (bleomycin, vincristin, cisplatin/etoposide, ifosfamide, and cisplatin).





**Figure 2.** Cumulative risk of cardiovascular risk factors overweight, hypercholesterolemia, and hypertension from start of chemotherapy (study I). Data are shown for patients in whom data on the concerned risk factors at start of chemotherapy are available.

development of cardiovascular risk factors (study I)

Assessments of overweight, hypercholesterolemia, and hypertension were available until a median follow-up of 9.1 years (range 0.2–28.9). At the last assessment, the prevalence of risk factors was BMI >27.8 kg/m<sup>2</sup> 85/359 (24%, new in 15% of the patients compared with prechemotherapy), hypercholesterolemia 87/361 (24%, new in 14%), and hypertension 106/359 (30%, new in 23%).

Figure 2 shows cumulative risks for the risk factors from the start of chemotherapy. Median time for the development of BMI >27.8 kg/m<sup>2</sup> is 1.7 years (range 0.2–28.4), for hypercholesterolemia 0.9 years (range 0.2–22.4), and for hypertension 5.1 years (range 0.2–21.2).

the metabolic syndrome and associated features (study II)

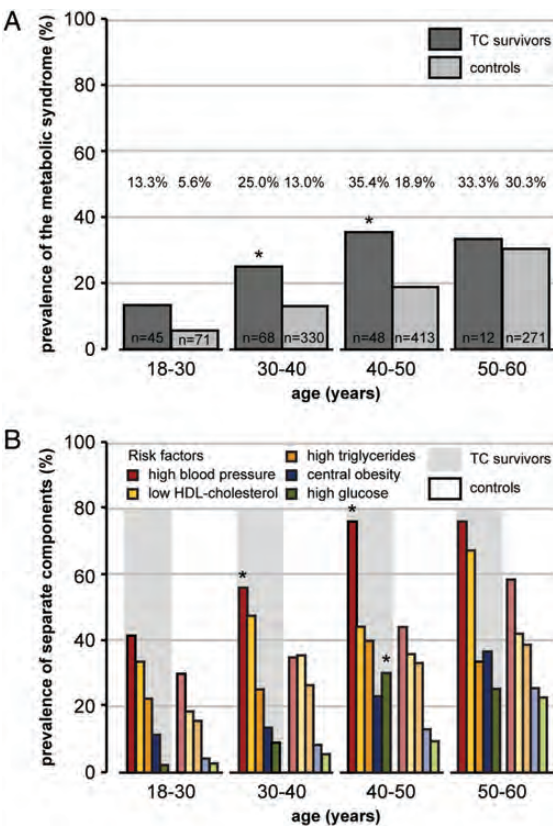
prevalence

At the median follow-up of 5 years (range 3–20) and attained age of 37 years (range 19–59), the prevalence of the MS was 44/173 (25%). The prevalence increases with ascending age, from 13.3% in survivors 18–30 years old to around 35% in survivors 40–60 years old (Figure 3A). High blood pressure is the most frequent component of the MS (59%), followed by low HDL cholesterol (44%), high triglycerides (29%), central obesity (17%), and high glucose levels (14%) (Figure 3B; Table 2). All components tend to increase in prevalence with age.

Adjusted for age, TC survivors show an increased risk of the MS compared with the general population with an odds ratio (OR) of 2.2 [95% confidence interval (CI) 1.5–3.3] (Table 2). This effect corresponds with 12.9 years' increase in age compared with the control population. TC survivors especially have an increased risk of high blood pressure (Table 2).

metabolic syndrome associated features

There is no difference in smoking behavior and family history for CVD between survivors with and without MS. Survivors



**Figure 3.** Prevalence of the metabolic syndrome in TC survivors and in controls according to age category (A) and prevalence of its separate components (B) (study II). \**P* < 0.05 compared with controls ( $\chi^2$  test).

**Table 2.** Prevalence of and risk for the metabolic syndrome and its separate components after chemotherapy for testicular cancer (study II, *N* = 173). The risks are expressed as age-adjusted OR compared with the control population with 95% CI and *P* value (binary logistic regression)

Dependent variables	Prevalence	OR	95% CI	<i>P</i>
Metabolic syndrome	44/173 (25%)	2.2	1.5–3.3	0.0001
Separate components				
High blood pressure	100/171 (59%)	2.5	1.8–3.6	<0.0001
Low HDL cholesterol	76/173 (44%)	1.7	1.2–2.3	0.003
High triglycerides	50/173 (29%)	1.2	0.8–1.7	0.424
Central obesity	29/170 (17%)	1.9	1.2–3.1	0.005
High glucose	24/170 (14%)	2.3	1.4–3.7	0.002

OR, odds ratios; 95% CI, 95% confidence interval; HDL, high density lipoprotein.

with MS have more central obesity, reflected by a higher waist/hip ratio, higher plasma leptin and lower plasma adiponectin, and increased HOMA-IR index (Table 3).

The association of MS with inflammation, prothrombotic state, endothelial activation, and signs of vascular damage was analyzed with adjustment for age. In presence of MS, prothrombotic are increased (Supplemental Table S1, available in *Annals of Oncology* online). The presence of MS is associated with lower BRS and increased carotid artery IMT

**Table 3.** Comparison between TC survivors with the metabolic syndrome and TC survivors without the metabolic syndrome with respect to survivor characteristics, cardiovascular risk factors, metabolic features, and gonadal function (study II)

Characteristics <sup>a</sup>	Metabolic syndrome present (44)	Metabolic syndrome absent (129)	P <sup>b</sup>
Survivor characteristics and cardiovascular risk factors			
Age at start chemotherapy (years)	29 (18–48)	26 (16–52)	0.086
Cumulative dose cisplatin (mg/m <sup>2</sup> )	421 (400–800)	406 (300–600)	0.22
Follow-up duration (years)	7 (3–20)	5 (3–20)	0.046
Age at study participation (years)	40 (23–57)	35 (19–59)	0.005
Smoking habits			
Current smoker	14/44 (32%)	51/128 (40%)	0.546
Ex-smoker	11/44 (25%)	24/128 (19%)	
Life-long nonsmoker	19/44 (43%)	53/128 (41%)	
Positive family history CVD	6/42 (14%)	17/123 (14%)	1.000
Metabolic features			
BMI (kg/m <sup>2</sup> )	28.4 (22.9–38.7)	24.0 (17.4–38.8)	<0.0001
Waist/hip ratio	0.99 (0.83–1.12)	0.92 (0.80–1.15)	<0.0001
Leptin (ng/ml)	12.77 (2.37–43.29)	3.71 (0.24–66.12)	<0.0001
Adiponectin (μg/ml)	5.00 (2.04–11.19)	7.23 (2.76–17.40)	<0.0001
HOMA-IR index	3.30 (1.56–23.86)	2.19 (0.20–2.04)	<0.0001
Gonadal function			
Testosterone supplementation	1/44 (2%)	8/129 (6%)	0.451
Total testosterone (nmol/l) <sup>c</sup>	15 (9–31)	18 (4–37)	<0.0001
Testosterone <15 nmol/l <sup>c</sup>	19/43 (44%)	17/121 (14%)	0.0002
FSH (U/l) <sup>c</sup>	16.80 (4.34–47.50)	13.90 (2.38–7.50)	0.452
LH (U/l) <sup>c</sup>	6.42 (2.47–18.70)	5.45 (1.59–33.10)	0.190

CVD, cardiovascular disease.

<sup>a</sup>Median (range) or n/N (%).<sup>b</sup>Mann–Whitney *U* test for continuous data and  $\chi^2$  test for categorical data.<sup>c</sup>For TC survivors not receiving testosterone supplementation.

(Supplemental Table S1, available in *Annals of Oncology* online).

### gonadal function

Median total testosterone level is lower in presence of MS [excluding survivors with testosterone supplementation (*N* = 9)] (Table 3; Supplemental Figure S1, available in *Annals of Oncology* online). A cutoff value of total testosterone <15 nmol/l was considered best discriminating for the MS [area under the ROC curve 0.65 (95% CI 0.55–0.74), area under the ROC curve of age 0.65 (95% CI 0.55–0.75)]. Unsupplemented total testosterone <15 nmol/l is associated with an age-adjusted OR of 4.1 (95% CI 1.8–9.3; *P* = 0.001) for the MS (Supplemental Table S2, available in *Annals of Oncology* online). Low testosterone shows association with central obesity [OR = 5.7 (95% CI 2.3–14.1); *P* < 0.001] and high glucose levels [OR = 2.9 (95% CI 1.1–7.5); *P* = 0.031].

## discussion

Our cross-sectional assessment of the MS (study II) shows that at the median follow-up of 5 years, 25% of the TC survivors have the MS. The syndrome shows an age-related increase in prevalence up to around 35% for survivors aged 40–60 years. A MS prevalence of 34% has recently been described after chemotherapy in a Norwegian cohort of TC survivors with a median age of 49 (range 31–69) years [15].

In this study, we show that the MS and its components central obesity, low HDL cholesterol, high blood pressure and high glucose levels are more prevalent in TC survivors than in the general population. The risk of the MS in TC survivors is 2.2 (95% CI 1.5–3.3) times higher than in the general population, corresponding with the risk of the MS in men aged 12.9 years. This suggests development of metabolic risk factors at earlier age.

Although we did not have retrospective data on the MS for our cohort of TC survivors, the regular assessment of cardiovascular risk factors during standard follow-up enabled us to evaluate the development over time of overweight, hypertension, and hypercholesterolemia as surrogate markers for the MS. Retrospective evaluation of the development of cardiovascular risk factors (study I) shows that overweight and hypercholesterolemia develop mainly within the first 5 years after platinum-based chemotherapy, after the median follow-up of 1.7 years for BMI > 27.8 kg/m<sup>2</sup> and 0.9 years for hypercholesterolemia. The cumulative risks of overweight and hypercholesterolemia show a plateau after a follow-up period around 10 years. In contrast, hypertension develops later, after the median follow-up of 5.1 years, and does not show a plateau with prolonged follow-up. The later appearance of hypertension may be related to its development secondary to other metabolic risk factors. Moreover, hypertension may reflect the long-term effect of direct chemotherapy-induced endothelial damage.

A considerable proportion of the TC survivors with overweight, hypercholesterolemia, or hypertension at the end of follow-up already had these risk factors at the start of chemotherapy. Unfortunately, it is unknown whether the prechemotherapy prevalence of these factors is representative for the age-matched general population because we do not have retrospective data for the controls used in this study. On the one hand, presence of cancer may contribute to lower cholesterol levels and lower BMI as previously described [16]. On the other hand, the MS is increasingly recognized as risk factors for the development of several cancer types [17] and may be consequently overrepresented in patients with cancer.

Although we have no longitudinal data on the cardiovascular risk factors in the general population, our data suggest that the MS develops at earlier age in TC survivors (study II) and that development of cardiovascular risk factors can already be observed during the first years of follow-up (study I).

In line with previous studies, we have found an association between total testosterone levels and MS in TC survivors [18, 19]. In the general population, low testosterone levels are predictive for the development of MS [20–22]. Our data show that survivors with unsupplemented total testosterone <15 nmol/l (22% of the evaluated survivors) have an approximately four times increased risk for the MS, particularly associated with central obesity. We hypothesize that decrease in testosterone levels and secondary central, visceral fat deposition has an important role in the development of the MS. Unsupplemented testosterone <15 nmol/l also shows an association with high glucose levels. This corresponds with the independent association of low to normal testosterone levels with insulin resistance, as observed in older men [23].

TC survivors with MS show features of central, visceral fat deposition: increased waist-to-hip ratio, elevated levels of leptin, decreased levels of adiponectin, and insulin resistance. Decreased adiponectin levels and increased fibrinogen levels are associated with an inflammatory state. Low-grade inflammation and prothrombotic state are closely linked in the pathobiology of atherosclerosis [24, 25]. The observed association with increased carotid IMT and decreased BRS underscores the potential clinical relevance of the MS in TC survivors. Increase in IMT is an accepted marker of early atherosclerosis [26] and decrease in BRS [27, 28] has also been associated with atherosclerosis. Both are considered unfavorable predictors for CVD.

Although our data suggest a role of the increased prevalence of cardiovascular risk factors in the development of CVD in TC survivors treated with platinum-based chemotherapy, prolonged follow-up is needed to assess whether subclinical signs of atherosclerosis eventually progress to overt CVD. The homogeneity of the study population, most survivors having been treated with the current standard regimen BEP, excludes analysis of direct toxic effects of chemotherapy on the vasculature. Cisplatin as well as bleomycin can induce endothelial damage [29–31]. As cisplatin in plasma remains detectable up to 20 years after chemotherapy [32] and may still be partially in reactive form [33], we hypothesize that there is an ongoing process of platinum-induced direct vascular toxicity.

The current observations on cardiovascular risk factors and MS in long-term TC survivors suggest that detection and

timely treatment from the start of chemotherapy and during the follow-up may contribute to a reduction in CVD risk. Overweight and hypercholesterolemia can be detected mainly within the first 5 years after chemotherapy. However, the risk for hypertension, which may also be a sign of developed vascular damage, extends beyond a follow-up period of 10 years. Therefore, extended follow-up seems necessary.

By implementing prolonged follow-up, it will become clear whether TC survivors with MS will have a higher CVD risk than TC survivors without MS, than individuals with MS in the general population. If previous treatment of TC turns out to be an additional cardiovascular risk factor, treatment indications for the MS may be more stringent for TC survivors. In addition, a randomized, placebo-controlled trial may help to evaluate whether testosterone supplementation contributes to prevention or treatment of MS in TC survivors. In other cancer survivors, i.e. after treatment of hematologic malignancies, early breast cancer, and prostate cancer, there are also signs of increased occurrence of the MS [34–38]. Although low testosterone levels with androgen deprivation are likely to be involved in the development of MS in prostate cancer survivors, for survivors of hematological malignancies and breast cancer, other mechanisms are involved. The more general interventions should be considered in the later patients.

In conclusion, the MS is more prevalent and appears to develop at earlier age in TC survivors treated with platinum-based chemotherapy compared with the general population. It is associated with subclinical, unfavorable changes in IMT and BRS, which may precede overt CVD. The early development of overweight and dyslipidemia advocates the development of guidelines on detection and treatment from the start of chemotherapy and during the follow-up. In addition, close collaboration with primary care physicians seems necessary with respect to extended follow-up and treatment of cardiovascular risk factors. Low testosterone and its association with central obesity appear to play a central role in the development of the MS and is a target for future intervention studies.

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## disclosure

The authors have declared no conflicts of interest.

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